Dokumenttyp: journal article

Autor(en) des Beitrags: Beuschlein, Felix; Fassnacht, Martin; Assié, Guillaume; Calebiro, Davide; Stratakis, Constantine A; Osswald, Andrea; Ronchi, Cristina L; Wieland, Thomas; Sbiera, Silvia; Faucz, Fabio R; Schaak, Katrin; Schmittfull, Anett; Schwarzmayr, Thomas; Barreau, Olivia; Vezzosi, Delphine; Rizk-Rabin, Marthe; Zabel, Ulrike; Szarek, Eva; Salpea, Paraskevi; Forlino, Antonella; Vetro, Annalisa; Zuffardi, Orsetta; Kisker, Caroline; Diener, Susanne; Meitinger, Thomas; Lohse, Martin J; Reincke, Martin; Bertherat, Jérome; Strom, Tim M; Allolio, Bruno

Titel des Beitrags: Constitutive activation of PKA catalytic subunit in adrenal Cushing's syndrome.

Abstract: Corticotropin-independent Cushing's syndrome is caused by tumors or hyperplasia of the adrenal cortex. The molecular pathogenesis of cortisol-producing adrenal adenomas is not well understood. We performed exome sequencing of tumor-tissue specimens from 10 patients with cortisol-producing adrenal adenomas and evaluated recurrent mutations in candidate genes in an additional 171 patients with adrenocortical tumors. We also performed genomewide copy-number analysis in 35 patients with cortisol-secreting bilateral adrenal hyperplasias. We studied the effects of these genetic defects both clinically and in vitro. Exome sequencing revealed somatic mutations in PRKACA, which encodes the catalytic subunit of cyclic AMP-dependent protein kinase (protein kinase A [PKA]), in 8 of 10 adenomas (c.617A>C in 7 and c.595_596insCAC in 1). Overall, PRKACA somatic mutations were identified in 22 of 59 unilateral adenomas (37%) from patients with
overt Cushing's syndrome; these mutations were not detectable in 40 patients with subclinical hypercortisolism or in 82 patients with other adrenal tumors. Among 35 patients with cortisol-producing hyperplasias, 5 (including 2 first-degree relatives) carried a germline copy-number gain (duplication) of the genomic region on chromosome 19 that includes PRKACA. In vitro studies showed impaired inhibition of both PKA catalytic subunit mutants by the PKA regulatory subunit, whereas cells from patients with germline chromosomal gains showed increased protein levels of the PKA catalytic subunit; in both instances, basal PKA activity was increased. Genetic alterations of the catalytic subunit of PKA were found to be associated with human disease. Germline duplications of this gene resulted in bilateral adrenal hyperplasias, whereas somatic PRKACA mutations resulted in unilateral cortisol-producing adrenal adenomas. (Funded by the European Commission Seventh Framework Program and others.)